

CLAIMS

1. An anti-EGFR polypeptide comprising at least one single domain antibody directed against EGFR.

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2. An anti-EGFR polypeptide according to claim 1 wherein at least one single domain antibody corresponds to a sequence represented by any of SEQ ID NOs: 1 to 22.

3. An anti-EGFR polypeptide according to claims 1 and 2 further comprising at least one single domain antibody directed against a serum protein.

10 4. An anti-EGFR polypeptide according to any of claims 1 to 3 further comprising at least one single domain antibody selected from the group consisting of anti-IFN-gamma single domain antibody, anti-TNF-alpha single domain antibody, anti-TNF-alpha receptor single domain antibody and anti-IFN-gamma receptor single domain antibody.

15 5. An anti-EGFR polypeptide according to any of claims 1 to 4, wherein the number of single domain antibodies directed against EGFR is at least two.

20 6. An anti-EGFR polypeptide according to any of claims 1 to 5 wherein at least one single domain antibody is a *Camelidae* VHH.

7. An anti-EGFR polypeptide according any of claims 1 to 6 wherein at least one single domain antibody is a humanised *Camelidae* VHH.

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8. An anti-EGFR polypeptide according to any of claims 1 to 7, wherein said single domain antibody is an homologous sequence, a functional portion, or a functional portion of an homologous sequence of the full length single domain antibody.

30 9. An anti-EGFR polypeptide according to any of claims 1 to 8, wherein the anti-EGFR polypeptide is an homologous sequence, a functional portion, or a functional portion of an homologous sequence of the full length anti-EGFR polypeptide.

35 10. A method of identifying an agent that modulates the binding of an anti-EGFR polypeptide of any of claims 1 to 9 to Epidermal Growth Factor Receptor:

(a) contacting a polypeptide according to any of claims 1 to 5 with a target that is Epidermal Growth Factor Receptor, or a fragment thereof, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and

5 (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator identified said candidate modulator as an agent that modulates the binding of an anti-EGFR polypeptide of any of claims 1 to 9 and Epidermal Growth Factor Receptor.

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11. A method of identifying an agent that modulates Epidermal Growth Factor Receptor mediated disorders through the binding of an anti-EGFR polypeptide of any of claims 1 to 9 to Epidermal Growth Factor Receptor comprising:

15 (a) contacting an anti-EGFR polypeptide according to any of claims 1 to 9 with a target that is Epidermal Growth Factor Receptor, or a fragment thereof, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and

20 (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator identified said candidate modulator as an agent that modulates Epidermal Growth Factor Receptor-mediated disorders.

25 12. A method of identifying an agent that modulates the binding of Epidermal Growth Factor Receptor to its receptor through the binding of an anti-EGFR polypeptide of any of claims 1 to 9 to Epidermal Growth Factor Receptor comprising:

30 (a) contacting an anti-EGFR polypeptide according to any of claims 1 to 9 with a target that is Epidermal Growth Factor Receptor, or a fragment thereof, or homologous sequence thereof, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and

35 (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator identified said candidate modulator as an agent that modulates the binding of Epidermal Growth Factor Receptor natural ligand.

13. A kit for screening for agents that modulate Epidermal Growth Factor Receptor - mediated disorders comprising an anti-EGFR polypeptide according to any of claims 1 to 9 and Epidermal Growth Factor Receptor, or a fragment thereof thereof.

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14. An unknown agent that modulates the binding of the polypeptides of claims 1 to 9 to Epidermal Growth Factor Receptor, identified according to the method of claim 10 to 128.

10 15. An unknown agent that modulates Epidermal Growth Factor Receptor-mediated disorders, identified according to the methods of claims 10 to 12.

16. An unknown agent according to claim 11 wherein said disorders are one or more of cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung.

15 17. A nucleic acid encoding a polypeptide of any of claims 1 to 9.

18. An anti-EGFR polypeptide according to any of claims 1 to 9 or a nucleic acid according to claim 17, or an agent according to any of claims 14 to 16 for treating and/or preventing and/or alleviating disorders relating to cancer, rheumatoid arthritis, psoriasis, or 20 hypersecretion of mucus in the lung.

25 19. Use of an anti-EGFR polypeptide according to any of claims 1 to 9 or a nucleic acid according to claim 17, or an agent according to any of claims 14 to 16 for the preparation of a medicament for treating and/or preventing and/or alleviating disorders relating to cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung.

30 20. An anti-EGFR polypeptide according to any of claims 1 to 9 for treating and/or preventing and/or alleviating disorders susceptible to modulation by the delivery of an EGFR antagonist that is able pass through the gastric environment without being inactivated.

35 21. Use of anti-EGFR polypeptide according to claims 1 to 9 for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by the delivery of an EGFR antagonist that is able to pass through the gastric environment without being inactivated.

22. A polypeptide according to any of claims 1 to 9 for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by the delivery of an EGFR antagonist to the vaginal and/or rectal tract without inactivation.

5 23. Use of a polypeptide according to claims 1 to 9 for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by the delivery of an EGFR antagonist to the vaginal and/or rectal tract without inactivation.

10 24. A polypeptide according to any of claims 1 to 9 for treating and/or preventing and/or alleviating disorders susceptible to modulation by the delivery of an EGFR antagonist to the upper respiratory tract and lung without inactivation.

15 25. Use of a polypeptide according to claims 1 to 9 for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders requiring the delivery of a therapeutic compound to the upper respiratory tract and lung.

20 26. A polypeptide according to any of claims 1 to 9 for treating and/or preventing and/or alleviating disorders susceptible to modulation by the delivery of an EGFR antagonist to the intestinal mucosa without inactivation, wherein said disorder increases the permeability of the intestinal mucosa.

25 27. Use of a polypeptide according to claims 1 to 9 for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by the delivery of an EGFR antagonist without inactivation, wherein said disorder increases the permeability of the intestinal mucosa.

30 28. A polypeptide according to any of claims 1 to 9 for treating and/or preventing and/or alleviating disorders susceptible to modulation by the delivery of an EGFR antagonist to the tissues beneath the tongue without inactivation.

35 29. Use of a polypeptide according to any of claims 1 to 9 for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by the delivery of an EGFR antagonist to the tissues beneath the tongue without inactivation.

30. A polypeptide according to any of claims 1 to 9 for treating and/or preventing and/or alleviating disorders susceptible to modulation by the delivery of an EGFR antagonist through the skin without inactivation.

5 31. Use of a polypeptide according to any of claims 1 to 9 for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by the delivery of an EGFR antagonist through the skin without inactivation.

10 32. A polypeptide, nucleic acid or agent according to claim 18, use of a polypeptide, nucleic acid or agent according to claim 19, a polypeptide according to any of claims 20, 22, 24, 26, 28 and 30, use of a polypeptide according to any of claims 21, 23, 25, 27, 29 and 31 wherein said disorders are cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung.

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33. A composition comprising a polypeptide according to any of claims 1 to 9 or a nucleic acid according any of claims 17, or an agent according to any of claims 14 to 16, and a suitable pharmaceutical vehicle.

20 34. A method of diagnosing a disorder characterised by the dysfunction of EGFR comprising:

- (a) contacting a sample with a polypeptide according to any of claims 1 to 9,
- (b) detecting binding of said polypeptide to said sample, and
- (c) comparing the binding detected in step (b) with a standard, wherein a difference in binding relative to said sample is diagnostic of a disorder characterized by dysfunction of EGFR.

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35. A kit for screening for a disorder cited in claim 34, using a method according to claim 30.

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36. A kit for screening for a disorder cited in claim 34 comprising an isolated polypeptide according to any of claims 1 to 9.

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37. Use of a polypeptide according to any of claims 1 to 9 for the purification of EGFR.

38. Use of a polypeptide of any of claims 1 to 9 for inhibiting the interaction between EGF and one or more EGFR.

39. A method for producing a polypeptide according to any of claims 1 to 9 comprising the 5 steps of:

- (a) obtaining double stranded DNA encoding a *Camelidae* species single domain heavy chain antibody directed to EGFR or a fragment thereof,
- (b) cloning and expressing the DNA selected in step (b).

10 40. A method of producing a polypeptide according to any of claims 1 to 9 comprising

- (a) culturing host cells comprising nucleic acid capable of encoding a polypeptide according to any of claims 1 to 9, under conditions allowing the expression of the polypeptide, and,
- (b) recovering the produced polypeptide from the culture.

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41. A method according to claim 40, wherein said host cells are bacterial or yeast.

42. A kit for screening for cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung, comprising a polypeptide according to claims 1 to 9.

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43. A therapeutic composition comprising:

- (a) a VHH which inhibits the growth of human tumor cells by said VHH binding to Epidermal Growth Factor Receptor of said tumour cell, and
- (b) an anti-neoplastic agent.

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44. A therapeutic composition of claim 43 for separate administration of the components.

45. A therapeutic composition of claims 43 and 44 wherein the cancer is selected from the group consisting of breast, ovary, testis, lung, colon, rectum, pancreas, liver, central 30 nervous system, head and neck, kidney, bone, blood and lymphatic system.